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A) FDA PRELIMINARY REQUIREMENTS FOR HEALTH CLAIMS

In order for a substance to be eligible for a health claim, it must meet the eligibility requirements of 21 CFR §101.14 as follows:

21 CFR §101.14 (b) Eligibility. For a substance to be eligible for a health claim:

(1) The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup (e.g., the elderly) is at risk, or, alternatively, the petition submitted by the proponent of the claim otherwise explains the prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet and satisfies the other requirements of this section.

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(3) If the substance is to be consumed at other than decreased dietary levels:

(i) The substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in Sec. 170.3(o) of this chapter, to the food and must retain that attribute when consumed at levels that are necessary to justify a claim; and

(ii) The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic

- 1) 21 CFR §101.14(b) (1) Dietary intake of green tea is associated with reduction in risk of cardiovascular disease.

The American Heart Association estimates that one out of every 5 deaths in the United States is directly attributable to Atherosclerotic Cardiovascular Disease (ASCVD), making it the leading cause of death in our country ⁽⁴⁾. There are also multiple lines of evidence from experimental animals, clinical investigations, epidemiological and randomized clinical trials supporting the strong causal relationship between individuals with hypercholesterolemia and ASCVD. In fact, this strong association of risk from Low Density Lipoprotein-Cholesterol (LDL-C) and cardiovascular disease has recently been reaffirmed as the primary goal of therapy by the National Cholesterol Education Program (NCEP) and is reflected in their latest guidelines called the Adult Treatment Panel III (ATP III) ^(5,6). Indeed, studies have shown that for each 1%

reduction in LDL-C, ASCVD risk is reduced by 1-2% (Gaziano *et al.*, 1996) ⁽⁷⁾. Dietary interventions shown to lower TC on average by 11% have been associated with significant reductions (21%) in mortality from CHD (ATP III).

With this in mind, the National Cholesterol Education Program (NCEP) revised previous dietary recommendations and called this diet Therapeutic Lifestyle Changes (TLC) (ATP III). TLC should always be the foundation of an approach to hypercholesterolemia. Specific recommendations include reducing saturated fat intake to < 7 % of calories, dietary cholesterol to < 200 mg/day, and increasing dietary viscous (soluble) fiber to 10-25 g/day while adding plant stanols/sterols (2 g/day) as therapeutic options to enhance LDL-Cholesterol lowering. Each of these therapies alone may reduce LDL-C by 5 -15% and thus can make an important contribution to ASCVD risk management in patients with hyperlipidemia. We will present data in this petition to support the inclusion of green tea with its active catechin components as another adjunct to this therapeutic approach in the management of risk factors associated with cardiovascular disease.

It has been demonstrated previously that excess LDL-C can be oxidized to ultimately form plaque that can build up on artery walls; restricting blood flow and elevating blood pressure. In turn, this can lead to CHD in those at risk, and if left untreated, to heart attack or stroke (Ross, 1999) ⁽⁸⁾. Indeed, Ross has provided an excellent review of atherosclerosis noting that it is more than just an accumulation of lipids within the arterial wall and is really an inflammatory disease. In this review, data are provided to support the hypothesis that response to injury occurring in atherosclerosis is due to endothelial dysfunction rather than denudation. Each characteristic lesion of atherosclerosis represents a different stage in a chronic inflammatory process in the artery; and if unabated and excessive, this process will result in an advanced, complicated lesion ultimately resulting in alteration of blood flow. This can ultimately lead to ischemia of the heart, brain, or extremities, resulting in infarction. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified LDL-C; free radicals caused by cigarette smoking, hypertension, diabetes mellitus; genetic alterations; elevated plasma homocysteine concentrations; infectious microorganisms such as herpes viruses or *Chlamydia pneumoniae*; and combinations of these or other factors. Vita (2003) ⁽⁹⁾ recently reviewed eight studies involving over 1500 subjects that examined endothelial dysfunction and an associated increased risk of cardiovascular events and all indicated that endothelial

dysfunction has prognostic value as a predictive indicator and appears to have utility as a biomarker or surrogate marker of cardiovascular risk. The evidence that green tea consumption has a beneficial effect on the vascular endothelium will be covered in the summary of scientific data.

Green tea is an excellent source of the catechin class of polyphenols, which as reducing agents, together with other dietary reducing agents, such as vitamin C, vitamin E and carotenoids, protect the body's tissues from oxidative stress. It is well known that oxidative damage to biomolecules has been implicated in the pathology of a number of chronic diseases, including cardiovascular diseases. The known *in vitro* antioxidant properties of catechins and other polyphenolic compounds in green tea have led to considerable interest by practitioners and consumers alike into the health benefits of their consumption and benefit on vascular endothelial homeostasis. This ability of green tea to act as a free radical scavenger will be presented as part of the summary of scientific data below.

The American Heart Association has recently provided heart disease and stroke statistics (www.americanheart.org/downloadable/heart/1105390918119HDSSStats2005Update.pdf). Of the more than 70 million Americans with one or more types of cardiovascular disease (CVD), 27 million are estimated to be age 65 or older. As the life expectancy of the US population continues to increase over the next 25 years, a result of improved nutrition, improved medical care, and increased awareness of environmental factors, the number of individuals suffering from chronic diseases including coronary artery disease, heart failure and stroke also will increase. The U.S. Census estimates that there will be 40 million Americans age 65 or older in the year 2010. According to these statistics, the average annual rates of first major cardiovascular events rise from 7 per 1,000 men at ages 35-44 to 68 per 1,000 at ages 85-94. For women, comparable rates occur 10 years later in life with the gap narrowing with advancing age.

As the above clearly demonstrates, a significant increase in the prevalence of age-related cardiac disorders in the U.S. is likely to be observed due to improvements in dietary, nutritional and lifestyle habits. Dietary patterns associated with risk factors for cardiovascular disease in healthy US adults include high intakes of processed meats, eggs, red meats, and high-fat dairy products. (Kerver *et al.*, 2003)⁽¹¹⁾. These patterns were also associated positively with serum C-peptide, serum insulin, and glycated hemoglobin and inversely with red blood cell folate concentrations.

In contrast to these negative dietary trends, there is an increased interest in the health benefits of foods and dietary supplements. This is largely associated with the maturing baby-boomers who are nearing retirement age and are becoming increasingly aware that health is a personal concern. One promising approach to providing consumer choices leading to healthier foods and which may reduce the risk of cardiovascular diseases is to incorporate substances in the diet that can positively impact a reduction in some of the known risk factors for this disease. Green tea with its naturally high level of polyphenolic compounds (the catechins) can be easily consumed as either a brewed or RTD beverage. It is well known that second to water, tea is the next highest consumed product in the world and enjoys wide appeal. By fully informing the consumer of the benefits by health claim labeling of green tea products, they will be able to select and easily incorporate green tea into their standard diet. In this manner, even for the consumers who did not markedly change their normal diet, the consumption of green tea would confer a positive health benefit including a reduction of risk for cardiovascular disease. In this manner, it is possible to deliver physiologically important and beneficial nutrients into the daily diet without having to overcome longstanding cultural food preferences in the general population.

2) 21 CFR §101.14(b) (3) (i) Green tea contributes and retains nutritive value as a conventional food

Under Sec. §101.14(b)(3)(i), the substance that is the subject of a health claim must contribute taste, aroma, or nutritive value, or any other technical effect listed in 21 CFR §170.3(o), to the food and must retain that attribute when consumed at the levels that are necessary to justify a claim. Green tea contributes taste, aroma, and nutritive value and has other technical effect listed in Sec. §170.3(o) as an antioxidant.

The term “nutritive value” is defined in Sec. §101.14(a) (3) as “value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy.” In the proposed rule entitled “Labeling; General Requirements for Health Claims for Food” (56 FR 60537, November 27, 1991), FDA proposed this definition and explained its interpretation of nutritive value in the context of whether a substance is a food and thus appropriately the subject of a health claim (56 FR 60537 at 60542). The agency indicated that the definition was formulated based on the common meaning of the words that make up the term “nutritive value.” The agency also added that use of the phrase “such processes as” in the definition of nutritive value was intended to provide a measure of flexibility that the agency

believed would be necessary in evaluating future petitions. In the final rule adopting the proposed definition, the agency noted that the evaluation of the nutritive value of substances would be done on a case-by-case basis to best ensure that the definition retains its intended flexibility (58 FR 2478 at 2488). In a subsequent final rule on health claims for dietary supplements (59 FR 395 at 407), FDA further explained that nutritive value “includes assisting in the efficient functioning of classical nutritional processes and of other metabolic processes necessary for the normal maintenance of human existence.”

A good working definition has been proposed for dietary antioxidants in a published National Academy of Sciences report, (2001)⁽¹¹⁾ titled Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids as follows:

“A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on the normal physiological function in humans.”

This definition and the expert reviews referenced above clearly support green tea meeting the Agency’s intended meaning of nutritive value in their use of the phrase “for nutritive value to include assisting in the efficient functioning of classical nutritional processes which are biochemically-based and of other metabolic processes necessary for the normal maintenance of human existence”. In addition to the green tea flavon-3-ol catechin components functioning as antioxidants, green tea also contains about 600 mg vitamin C and 80 mg vitamin E per 100 grams of dried leaves.

This antioxidant function of green tea is retained at the level proposed for use in brewed or RTD beverage and at the levels of catechins proposed for a product to qualify for the proposed qualified health claim.

3) 21 CFR §101.14(b) (3) (ii) Green tea is safe and lawful under the FDCA.

Green tea is brewed with natural tea leaves of *Camellia sinensis* and is generally recognized as safe (GRAS) pursuant to Section 409 of the Federal Food, Drug and Cosmetic Act and the regulations of the Federal Food and Drug Administration promulgated thereunder, particularly 21CFR §182.20.